NTP Research Concept: Butterbur

Project Leader:
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Nomination Background and Rationale:
Butterbur was nominated by the National Institute of Environmental Health Sciences (NIEHS) for comprehensive toxicological characterization based on its widespread use as a dietary supplement, suspicion of contamination with toxic pyrrolilzidine alkaloids, and lack of toxicity data on other constituents of Butterbur preparations. Additionally, there is insufficient data to determine if there is additional risk of adverse effects in pregnant or nursing mothers, especially with evidence from one clinical case report of fetal death as the result of maternal consumption of Butterbur.

Butterbur is the common name for the plant *Petasites hybridus* which is marketed as a dietary supplement. Extracts of this plant are available through internet sales as capsules, extracts, powders, tinctures, and softgels. Butterbur has been marketed for the treatment of migraines and tension headaches, spasms of the urogenital and digestive tracts, asthma, allergic rhinitis, gastric ulcers, and dysmenorrhoea. It is also being used to treat pain, upset stomach, chronic cough, chills, anxiety, plague, fever, insomnia, wounds, whooping cough, inflammatory bowel disease, chronic uticaria, and psoriasis. Clinical trials suggest that Butterbur use may be effective in treating allergic rhinitis and migraines; however, there was no clear evidence of effectiveness in the treatment of asthma or other disorders. The amount of Butterbur consumed in the U.S. is not publically available. Typical doses vary depending on manufacturer; however, it appears that a daily dose of 100-400 mg of butterbur extract is not uncommon.

Butterbur is manufactured by extraction of the rhizomes or aerial parts of *Petasites* species. Preparations of the extracts of Butterbur from rhizomes have been shown to contain many components including petasin, isopetasin, and neopetasin. Essential oils have been shown to contain petasitene and pethybrene. There has been some standardization of *Petasites* extracts to contain at least 7.5 mg of petasin and isopetasin per 50 milligram of extract (15 weight-percent).

Extraction methods have been developed to avoid co-extraction of pyrrolizidine alkaloids along with the desired plant products. The pyrrolizidine alkaloids senecionine and integerrimine have been detected in extracts of *Petasites* spp. plants. Pyrrolizidine alkaloids are metabolized by cytochromes P450 to a common active intermediate that is capable of covalently binding to DNA. Many pyrrolizidine alkaloids are carcinogenic in animal bioassays and are suspected of being human carcinogens.

There is a paucity of toxicological data on Butterbur preparations. Acute studies in Wistar rats established a maximally tolerated acute dose as $\geq$2.5 g/kg body weight, while intraperitoneal injection resulted in an LD_{50} value of 1 g/kg (data unpublished).

Extracts prepared from *Petasites japonicus* have been tested for beneficial/protective effects in rodents. Pretreatment of mice with methanolic extracts blocked kainic acid neurotoxicity in mice. Butterbur also reduced neurobehavioral effects of kainic acid, blocked developmental seizures, increased brain glutathione levels, and reduced peroxidation. Extracts of Butterbur have been shown to inhibit leukotriene synthesis and COX-2 and PGE-2 release in cells *in vitro*, and inhibit gastric damage from ethanol and indomethacin in rats *in vivo*.

Some of the individual components isolated from *Petasites* species plants have been shown to be toxic *in vivo*. Petasin and isopetasin have been reported to have effects on the cardiac system including decreased heart rate, decreased atrium contractions, and smooth muscle vasorelaxation through calcium channel modifications. Petasin and isopetasin may modulate endocrine function and have been shown to decrease plasma testosterone levels.

There are no reported studies on the reproductive toxicity, perinatal toxicity, or immunotoxicity effects of Butterbur preparations, and no reports of the effects of chronic consumption in rodents or other species.

Key Issues:
Butterbur is marketed for a variety of human disorders with a range of doses and duration of exposure. There are no data in the public literature to indicate that consistent plant sources (*e.g. P. japonicus*, *P. hybridus*, *P. officinalis*) are used for the preparation of Butterbur. Although extraction methods have been developed to minimize the presence of pyrrolizidine alkaloids in Butterbur preparations, there are no data to document the level of exposure of humans to pyrrollizidine alkaloids from Butterbur preparations. As a result, one key issue for toxicity testing is an understanding of the composition of the products marketed as Butterbur.

A second key issue is the potential toxicity of Butterbur when consumed during pregnancy. A single case report of a human fetal death and a lack of any additional toxicity data highlight the need for data to understand the extent of developmental and reproductive toxicity of Butterbur components.

A third key issue is the lack of published toxicity data. Insufficient data exist on reproductive and developmental toxicity, neurotoxicity, and carcinogenicity of Butterbur.

Proposed Approach:
In collaboration with the U.S. Food & Drug Administration, the NTP will conduct analytical chemical characterization of the products marketed as Butterbur. The survey will focus on quantification of the species of *Petasites* (*e.g.* contribution of *P. japonicus*, *P. hybridus*, *P. officinalis*) used in the production of Butterbur, and quantification of the major constituents of Butterbur including petasin, isopetasin, other sesquiterpenes (*e.g*. petasitene and pethybrene), and pyrrolizidine alkaloids (*e.g*. senecionine and integrrimine).

Toxicological characterization of the Butterbur preparation will be conducted using a tiered approach to maximize integration of data into subsequent study designs. *In vitro* genotoxicity, and where appropriate high throughput screening, will be conducted on extracts of the Butterbur preparation. Acute and subchronic toxicity studies will be conducted in rats and mice, with particular attention to the possibility of hepatotoxicity, neurotoxicity, and cardiotoxicity. Developmental and reproductive studies will be conducted in Sprague-Dawley rats. A two-year chronic toxicity study in rats and mice will be conducted to determine the risk of long-term exposure to Butterbur preparations.

Significance and Expected Outcome:
There is very little information on the toxicity of Butterbur which is marketed as a dietary supplement and herbal product. There is no data on the toxicity of as the result of extended use of Butterbur. These proposed studies will address inadequacies in the data regarding the toxicity of Butterbur products that are marketed in the U.S., and will provide information needed by the FDA in making decisions regarding the safety of Butterbur.